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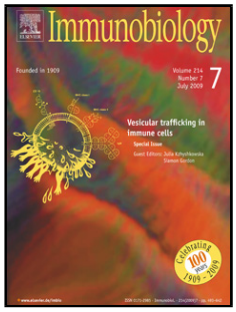

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Role of the lectin complement pathway in kidney transplantation

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Abstract

In the last 15 years two major advances in the role of complement in the kidney transplant have come about. The first is that ischaemia reperfusion injury and its profound effect on transplant outcome is dependent on the terminal product of complement activation, C5b-9. The second key observation relates to the function of the small biologically active fragments C3a and C5a released by complement activation in increasing antigen presentation and priming the T cell response that results in transplant rejection. In both cases local synthesis of C3 principally by the renal tubule cells plays an essential role that overshadows the role of the circulating pool of C3 generated largely by hepatocyte synthesis. More recent efforts have investigated the molecules expressed renal tissue that can trigger complement activation. These have revealed a prominent effect of collectin-11, a soluble C-type lectin that is expressed in renal tissue and aligns with its major ligand L-fucose at sites of complement activation following ischaemic stress. Biochemical studies have shown that interaction between CL-11 and L-fucose results in complement activation by the lectin complement pathway, precisely targeting the innate immune response to the ischaemic tubule surface. Therapeutic approaches to reduce inflammatory and immune stimulation in ischaemic kidney have so far targeted C3 or its activation products and several are in clinical trials. The finding that lectin-fucose interaction is an important trigger of lectin pathway complement activation within the donor organ opens up further therapeutic targets where intervention could protect the donor kidney against complement.

Keywords: Complement
Transplantation
Ischaemia reperfusion injury
Kidney
Innate immunity

Introduction

Complement is a major effector system which is comprised of numerous fluid-phase and membrane-bound protein receptors that interact rapidly and efficiently to clear invading pathogens. In this capacity, it is one of the main defence mechanism of the innate immune system. This paradigm has shifted significantly in the last decade or so, as complement is now known to interact closely with and indeed help direct alloimmune responses to solid organ transplants: not only does complement contribute to the damage associated with ischaemia reperfusion injury but it is also critical in both T cell-mediated and antibody-mediated rejection (Sacks and Zhou, 2012). Activation of the complement system is well-recognised as a key effector that mediates antibody-mediated rejection, as evidenced by the characteristics of donor-specific antibodies against MHC molecules (Loupy, et al., 2013). In solid organ transplantation, complement can directly damage the organ by coordinating the innate immune response associated with tissue hypoxia and oxidative stress, and can stimulate and modulate the specific anti-donor immune response. Additionally, recent evidence points to complement activation as a significant factor in the progression of chronic kidney disease (Fearn and Sheerin, 2015). From a clinical perspective, therapies that target effector functions of the complement system could be tailored more specifically if the key initiators of complement activation can be identified. This provides scope for guiding the development of intervention therapies that do not interfere with the anti-microbial effector functions of complement, such as opsonisation, cell lysis and the recruitment of inflammatory cells such as neutrophils (Ricklin, et al., 2010). In this article, we shall focus on current observations relating to the role of complement in post-ischaemic injury and allograft rejection, emphasising new concepts surrounding the emerging contribution of the lectin pathway of complement activation to organ injury, and provide insights into potential new endogenous ligands that may serve as useful targets for the design of therapies that aim to prevent injury and extend graft survival.

Complement activation and effector mechanisms

Activation of the complement cascade is triggered by three main pathways, i.e. the classical, lectin and alternative pathways (Walport, 2001). All three pathways converge at the formation of the pivotal complement component C3, which is subsequently cleaved leading to the formation of C5 convertase and the eventual recruitment of terminal complement components to form the terminal complement complex (C5b-9). Under normal physiological conditions, the activation of complement is tightly controlled by both surface-bound and soluble proteins. These protective mechanisms rely on enhancing the degradation of a variety of convertases thereby preventing the formation of MAC. Under inflammatory conditions, these protective mechanisms are overcome, which can happen

during solid organ transplantation, leading to uncontrolled complement-mediated injury and rejection (Yamanaka, et al., 2016). In the kidney and other solid organs, ischaemia-reperfusion (I/R) injury is an inevitable consequence of transplantation and post-ischaemic renal dysfunction is strongly dependent on the local conversion of C3 into its activated form (Zhou, et al., 2000). Thus, it has been established that renal tubule cells are not only capable of producing complement proteins (Peake, et al., 1999) but also that kidney-derived C3 is a mediator of localised injury and cell death (Farrar, et al., 2006) and provides a stimulus to T cell-mediated renal allograft rejection in both mice (Pratt, et al., 2002) and humans (Tang, et al., 1999). Downstream of C3 cleavage, C3a and C5a interact with their respective receptors on donor parenchymal cells and infiltrating leucocytes (Peng, et al., 2012) to mediate reperfusion injury. Engagement of C5aR on dendritic cells and T cells modulates the activation/function of these cells and consequently up-regulates the allospecific T cell responses, leading to allograft rejection (Li, et al., 2010). The finding that renal I/R injury led to parenchymal formation of C5b-9, suggested a contribution of the alternative pathway (Thurman, et al., 2003). This observation implied that classical or lectin pathway is needed to trigger the alternative pathway but recent findings indicate the lectin pathway is the principal initiator of complement activation and consequent tissue injury within the kidney (Farrar, et al., 2012).

The Lectin Pathway

The lectin pathway (LP) of complement activation is initiated when one of a number of well-characterized molecules known as pattern recognition receptors (PRRs) binds to pathogen-associated molecular patterns (PAMPs) that are displayed on the surface of invading microorganisms, or bind damage-associated molecular patterns (DAMPs) on endogenous ligands during inflammation (Genster, et al., 2014). Currently described LP activation molecules include the collagen-containing soluble C-type lectins (collectins), such as kidney collectin-11 (CL-K1) (Selman and Hansen, 2012), mannose-binding lectin (MBL) (Thiel, 2007) and surfactant proteins SP-A and SP-D (Waters, et al., 2009). Ficolins constitute another subset of LP activating molecules that consist of an N-terminal collagen-like domain and a terminal fibrinogen-like domain (Endo, et al., 2011). Collectins circulate as complexes with MBL-associated serine proteases (MASPs), of which there are three, named MASP-1, MASP-2, and MASP-3 (Dahl, et al., 2001, Thiel, et al., 1997) . Complement activation is initiated when these pre-formed complexes of collectins and MASPs bind to pathogens or endogenous ligands (Wallis, 2007).

Lectin Pathway in organ injury

MASP-2 activity is an absolute requirement for activation of the LP, with the traditional view being that MASP-2-mediated cleavage of C4 and C2 generates the classical C3 convertase C4b2a. However, a recent study has revealed a C4-independent bypass lectin activation pathway (Schwaeble, et al., 2011). In models both of cardiac and intestinal I/R injury, MASP-2 was found to be essential to mediate injury, even in the absence of C4. This suggested that the lectin pathway can cleave C3 without using the classical pathway components C4 and C2. In a further study, with a renal isograft model in wild type and MASP-2-deficient mice, absence of the serine protease was shown to reduce kidney injury; again, the protective effect was shown to be independent of C4, highlighting the importance of the C4-bypass route triggered by the LP in mediating tissue injury (Asgari, et al., 2014). Moreover, the findings help to account for other observations in the kidney, where absence of C4 in both native ischaemia (Zhou, et al., 2000) and renal allograft rejection (Lin, et al., 2006), failed to give protection from injury. Hence, in the heart as well as the kidney, there appears to be present a novel mechanism of LP activation. These findings raise questions as to what may be the initiating trigger of the LP of complement activation during ischaemia which is associated with whole organ transplantation.

Mannan binding lectin (MBL) in reperfusion injury

A role for MBL in renal and cardiac IR injury has been suggested. A study performed in mice and humans found that deposits of Mbl-1 and Mbl-2 co-localized with complement C3 (de Vries, et al., 2004). In a further study, mice deficient for both MBL-A and MBL-C displayed blunted ischaemic injury that was reversed following administration of recombinant MBL (Moller-Kristensen, et al., 2005). In a separate study, serum-derived MBL was found deposited with C3b on highly glycosylated zinc metalloproteases (meprins α and β) within ischaemic mouse kidney (Hirano et al, 2012). Furthermore, in a rodent model of cardiac ischaemia, both MBL and C3 deposition were found following the induction of ischaemia (Collard, et al., 2000). Though these studies suggest that MBL mediated the observed pattern of injury, a contribution of the classical pathway as a mediator of injury could not be ruled out. As well as binding carbohydrates on microorganisms, MBL is known to bind to carbohydrate moieties on certain immunoglobulin subclasses, namely IgA (Roos, et al., 2006) and IgM (McMullen, et al., 2006). Further investigation in ischaemic heart unveiled a pathophysiology that was dependent upon the interaction of both naturally-occurring IgM and mannose-binding lectin (Busche, et al., 2009) but with no involvement of the classical pathway (Walsh, et al., 2005). Further evidence for LP involvement in the presence of bound immunoglobulin derives from a model of ischaemic skeletal injury, in which naturally-occurring self-reactive IgM was identified to play a part in the injury (Zhang,

et al., 2004). This IgM has since been found to bind the self-antigen non-muscle myosin heavy chain type II (Zhang, et al., 2006) and the actin cytoskeleton (Shi, et al., 2009).

In human renal allograft rejection however, the evidence for MBL participation has been somewhat conflicting. With the prediction that higher MBL levels may be associated with increased complement-mediated allograft injury, a study showed that higher pre-transplant levels of MBL were found to be associated with more severe kidney rejection (Berger, et al., 2005). In a second study in which patients with type I diabetes and renal failure received a simultaneous pancreas and kidney transplant, patients with gene polymorphisms associated with lower levels of MBL had improved survival rates (Berger, et al., 2007). A number of studies have demonstrated contrasting findings, however. In a recent study, a large number of donor-recipients pairs were profiled for genes including *MBL-2* and *MASP-2* and it was clearly determined that the *MBL-2/MASP-2* genotypes had no association with graft outcome (Damman, et al., 2012). Whereas that study showed no correlation, other groups have observed an inverse correlation between MBL and graft outcome: in non-HLA-sensitized patients, a low serum level of MBL was found to be associated with a decrease in the 5-year survival rate of renal allografts (Bay, et al., 2013). It was speculated that the difference between outcomes observed in different centres could be explained by difference in laboratory antibodies and assays employed to generate data sets (Damman and Seelen, 2013). In a more recent study, low pre-transplant levels of MBL in renal transplant recipients correlated with increased severity of renal inflammation and an increase in tubular cell necrosis (Ibernon, et al., 2014). Similarly, in a Swiss study, it was determined that *MBL-2* polymorphisms resulted in low serum MBL levels which was associated with poor graft outcome (Golshayan, et al., 2016).

Ficolins in reperfusion injury

In humans three ficolins are described (Genster, et al., 2014), namely ficolin-1, ficolin-2 and ficolin-3. Only a limited number of studies have examined the role of ficolins in human allograft rejection. In a study investigating lectin gene profiles of over 1200 donor and recipient pairs, analysis of ficolin-2 gene haplotypes showed no association with allograft survival (Damman, et al., 2012). However, other reports have documented conflicting findings. For example, a common functional polymorphism in the ficolin-2 gene was found to be associated with a lower incidence of renal transplant rejection. The authors concluded that the polymorphism led to more efficient phagocytosis of damaged tissue with concurrent dampening of alloimmune responses (Eikmans, et al., 2012). High pre-transplant levels of

the most abundant ficolin in serum, ficolin-3, shows a strong association with poor allograft survival after kidney transplantation (Bay, et al., 2013, Smedbraten, et al., 2015).

What triggers MASP-2-dependent complement-mediated reperfusion injury?

It has been conclusively demonstrated in rodent models of reperfusion injury both for native and transplanted organs that MASP-2 is a key mediator of pathology (Asgari, et al., 2014, Farrar, et al., 2006, Schwaeble, et al., 2011). This raises the question as to which collectin preferentially triggers MASP-2 to initiate complement activation. As discussed above, there are several candidate lectins that could interact with MASP-2 at the site of tissue injury. However, in the case of MBL, synthesis primarily takes place in hepatocytes and it exists in the serum as oligomers with large molecular mass, which could limit the interaction between MBL and target structures in the extravascular compartment following I/R insult. This therefore raises the possibility of a role for the recently described PRR known as collectin-11 (CL-11), which is reported to be locally expressed within a number of organs.

Collectin-11

Collectin-11 (CL-11; also known as Collectin Kidney-1, CL-K1) is a recently described component of the innate immune system (Keshi, et al., 2006). Like MBL, the structure of CL-11 consists of a globular head that forms oligomers of 100 to 200 kDa (Selman and Hansen, 2012) and associates with MASPs via binding motifs within its collagenous portion (Ma, et al., 2013). It is synthesized by most tissues, including the liver, brain and heart, with significant production assigned to the kidney (Farrar, et al., 2016, Keshi, et al., 2006, Selman and Hansen, 2012). CL-11 is known to have significant interaction with bacteria (Hansen, et al., 2010, Ma, et al., 2013), indicating a significant role in host defence against pathogens and the carbohydrate recognition domain is known to bind a number of moieties, showing a preference for L-fucose (Keshi, et al., 2006). Interestingly, it has recently been demonstrated that CL-11 displays strong binding to nucleic acids and hence may have a role in the clearance of apoptotic cells following inflammatory damage (Henriksen, et al., 2013). Indeed, CL-11 is likely to be a significant component of inflammatory responses, since a recent study conducted in over 500 patients with disseminated intravascular coagulation (DIC) - a disorder associated with immune system activation - found that circulating serum levels of CL-11 were approximately two-fold above the normal range (Takahashi, et al., 2014).

Collectin-11 as a trigger of renal epithelial inflammation

The kidney tubule cell appears to be the main source of CL-11 in normal renal tissue and the level of expression is markedly elevated following renal I/R stress (Farrar, et al., 2016). In this context, CL-11 and the complement activation product C3d were found co-localised along the renal tubule basolateral surface in the hypoxia-sensitive zone of inner renal cortex, in close association with L-fucose. L-fucose is a preferred ligand for CL-11 in man and mouse (Farrar, et al., 2016, Selman and Hansen, 2012) and a component of many glycans that are produced by renal epithelial cells and are expressed at the cell surface, making it very likely that lectin pathway involvement in this injury is triggered by CL-11 (**Figure 1**).

This is further supported by the finding that mice with gene deleted CL-11 were found to be resistant to post-ischaemic renal failure and associated complement-mediated damage. The mechanism appears to involve the expression of an abnormal pattern of fucosylated cell surface ligand following hypoxic insult, which induces CL-11 attachment followed MASP-2-mediated complement activation, based on ex vivo analysis in renal tubule cells (Farrar, et al., 2016). Experiments with transplanted kidney confirmed the importance of locally derived CL-11 in injury induced by cold ischaemic insult, suggesting that it should be possible to engineer protection by pharmacologically blocking the collectin-ligand interaction site on the donor organ. The broader implication of these findings in other inflammatory conditions and tissue sites remains to be determined.

Concluding remarks

Clinical trials will tell if complement is a viable therapeutic target for improving the outcomes of renal transplantation, and several relevant trials are currently in progress. One of the key questions concerns where to inhibit complement: C3 or C5. Recent studies have provided a clearer signal that the lectin pathway is involved, thereby identifying an additional and more proximal intervention site in the early pathogenic response to ischaemic stress. This is an ever pressing question for renal transplantation, given the need to use donor organs that have a substantial risk of ischaemic injury. Precision treatment targeted to the appropriate complement subcomponent and tissue compartment will depend on clear understanding of the molecular and cellular mechanisms in each type of pathology. This seems increasingly to implicate a role for the lectin pathway and related tissue ligands.

Conflict of Interest

None declared.

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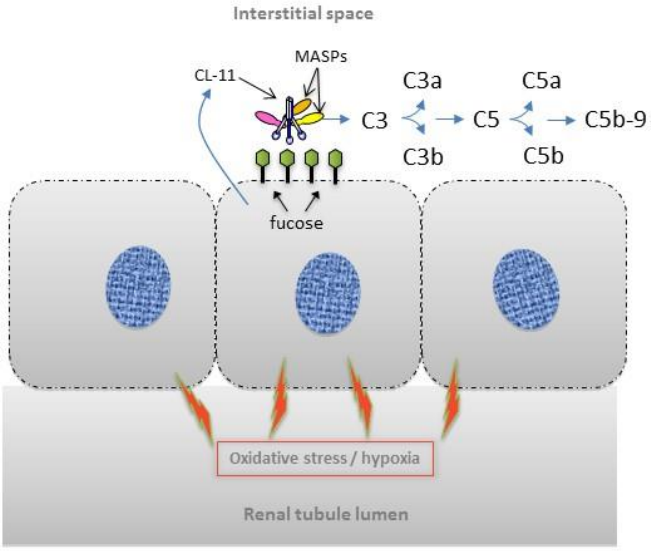

Figure 1. Implied mechanism of complement-mediated injury in transplanted kidney. Stressed renal tubule cell expresses aberrant pattern of fucosylated ligand resulting in cell surface engagement of collectin-11 (CL-11) and consequent lectin complement pathway mediated cleavage of C3. Terminal pathway effectors C5a and C5b-9 mediate post-ischaemic tubule injury, while anaphylatoxins C3a and C5a enhance alloantigen presentation and T cell recognition to promote graft rejection. Exclusive expression L-fucose in the presence of CL-11 and C3 predispose the proximal tubule cell to post-renal transplant injury.